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Pulmonary mucosa-associated lymphoid tissue lymphoma: insights from a 15-year study at a single institution involving 14 clinical cases

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Abstract

Objective This study aims to delineate the clinical presentations, imaging features, pathological characteristics, therapeutic strategies, and outcomes of pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma, thereby deducing the most efficacious treatment paradigm.

Methods We conducted a retrospective review of 14 patients diagnosed with pulmonary MALT lymphoma at the Second Xiangya Hospital, affiliated with Central South University, between September 2007 and September 2022, focusing on their clinical profiles, diagnostic pathways, treatment modalities, and prognostic outcomes.

Results The cohort's median age was 60 years (ranging from 44 to 81 years), with 64.29% being female and only 14.29% having a history of smoking. The incidence of immunodeficiency diseases among the patients was notably low. Imaging typically revealed pulmonary nodules and masses, with air bronchogram signs evident in 9 patients and pleural effusion in 2. CD20 expression was markedly positive across the board in all patients with pulmonary MALT lymphoma. Among the 12 patients who received intervention, 6 were treated with chemotherapy alone, 2 underwent surgical resection, and 4 benefitted from a combined approach of chemotherapy and surgery. Over the monitoring period, 2 patients succumbed to their disease. The estimated 5- and 10-year overall survival (OS) rates were 91.67% and 76.39%, respectively, with the median progression-free survival (PFS) reaching 7 years. Comparative analysis revealed no significant disparity in PFS between patients treated exclusively with chemotherapy and those receiving both chemotherapy and surgical intervention ($P=0.22$).

Conclusion Pulmonary MALT lymphoma typically exhibits a slow course, with gradual progression and a predominantly positive prognosis. Chemotherapy emerges as the preferred therapeutic option for managing this malignancy.

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Introduction

Primary pulmonary non-Hodgkin's lymphoma is a rare type of extranodal lymphoma, accounting for about 0.4% of lymphoma incidence and 0.5% of primary malignant tumors of the lung [1, 2]. Among them, mucosa-associated lymphoid tissue (MALT) lymphoma is the most common type of primary pulmonary lymphoma, also known as extranodal marginal zone B-cell lymphoma, accounting for approximately 70-80%. Pulmonary MALT lymphoma can originate from any mucosal site, with the lungs often being the most affected organ, especially the MALT of the bronchi [3–5].

A significant proportion of patients with pulmonary MALT lymphoma remain asymptomatic; symptomatic individuals often exhibit nonspecific pneumonia-like symptoms, including dyspnea, chest pain, cough, and sputum production. Notably, pulmonary MALT lymphoma has a propensity to stay localized at the initial site of development for prolonged durations, leading to a protracted history of localized disease. This tendency greatly complicates accurate clinical diagnosis, rendering pulmonary MALT lymphoma a diagnostic challenge in clinical settings [6, 7]. Chest radiography and computed tomography (CT) scans serve as primary diagnostic tools, with the former generally revealing well-defined isolated nodules and the latter displaying single or multiple nodules or lung consolidation areas [8].

Treatment strategies for pulmonary MALT lymphoma primarily encompass chemotherapy, surgical resection, and adjunctive chemoradiotherapy post-surgery. However, the rarity of this condition has resulted in a dearth of prospective studies addressing its diagnosis and treatment. Although numerous case reports exist, comprehensive guidelines for the diagnostic and therapeutic management of pulmonary MALT lymphoma remain elusive. Consequently, this study aims to elucidate the clinical features and therapeutic outcomes of 14 patients with pulmonary MALT lymphoma, treated at our institution from September 2007 to September 2022, as detailed herein.

Materials and methods

General data

This retrospective study is based on clinical, radiological, and pathological data from 24 cases of pathologically confirmed pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma at the Second Xiangya Hospital, affiliated with Central South University, between September 2007 and September 2022. The collected data encompassed a range of variables, including patients' gender, age, performance status (PS), medical history, clinical presentations, hemoglobin levels, CT imaging results, histopathology, treatment approaches, outcomes, and mortality causes. The diagnostic foundation for pulmonary MALT lymphoma was established through bronchoscopic biopsy ($n=15$), surgical excision ($n=6$), and CT-guided percutaneous lung biopsy ($n=3$). Inclusion Criteria: (1) Pathological confirmation of pulmonary MALT lymphoma, adhering to the World Health Organization's guidelines for diagnosing primary lung site MALT lymphoma [9]; (2) Chest CT indicative of patchy consolidation within the lung parenchyma. Exclusion Criteria: (1) Substandard imaging quality ($n=3$); (2) Incomplete pathological review (e.g., absent clinical pathological staging) ($n=3$); (3) Various other reasons (e.g., missing outcome data, lost for follow-up) ($n=4$). Consequently, 14 patients were eligible for this study, comprising 5 males and 9 females, aged between 44 and 81 years, with a mean age of 60.71 ± 12.54 years (Fig. 1). The institutional ethics committee granted approval for this study.

Imaging examination methods

All 14 participants underwent standard chest CT scans using a 64-slice spiral CT scanner, covering the thoracic cavity from apex to the bilateral adrenal glands. The scans had a 5 mm slice thickness and a 5 mm interval between slices. For contrast-enhanced scans, an iodinated contrast medium (130 mg I/mL) was administered intravenously at a rate of 3.0-3.5 mL/s using a high-pressure injector. The contrast enhancement (ΔCT value=CT value after contrast enhancement - CT value before contrast enhancement) was assessed by manually selecting the region of interest (ROI) on the tumor's largest cross-section, typically spanning 80–100 mm^2. Radiologists assessed the average change in CT values (ΔCT) before and after contrast enhancement on the same image layer. ΔCT refers to the change in CT values (Δ indicates "change" or "difference"). In imaging, ΔCT is typically used to represent the difference in CT values measured under specific conditions, such as before and after contrast agent injection.

Imaging examination analysis

The degree of enhancement was categorized based on the increase in CT values: 0–20 HU as mild, 20–40 HU as moderate, and over 40 HU as severe enhancement. The images were evaluated with the CT characteristics of the lesions, focusing on their distribution, location, size, shape, density, and enhancement patterns.

Statistical methods

Data were analyzed using SPSS software, version 22.0. We employed the Kaplan-Meier method to generate progression-free survival (PFS) and overall survival (OS) curves. Cases still alive or without disease progression as of the last follow-up (censored on September 30, 2023) were considered censored. The observation period extended from the date of confirmed diagnosis to either the last

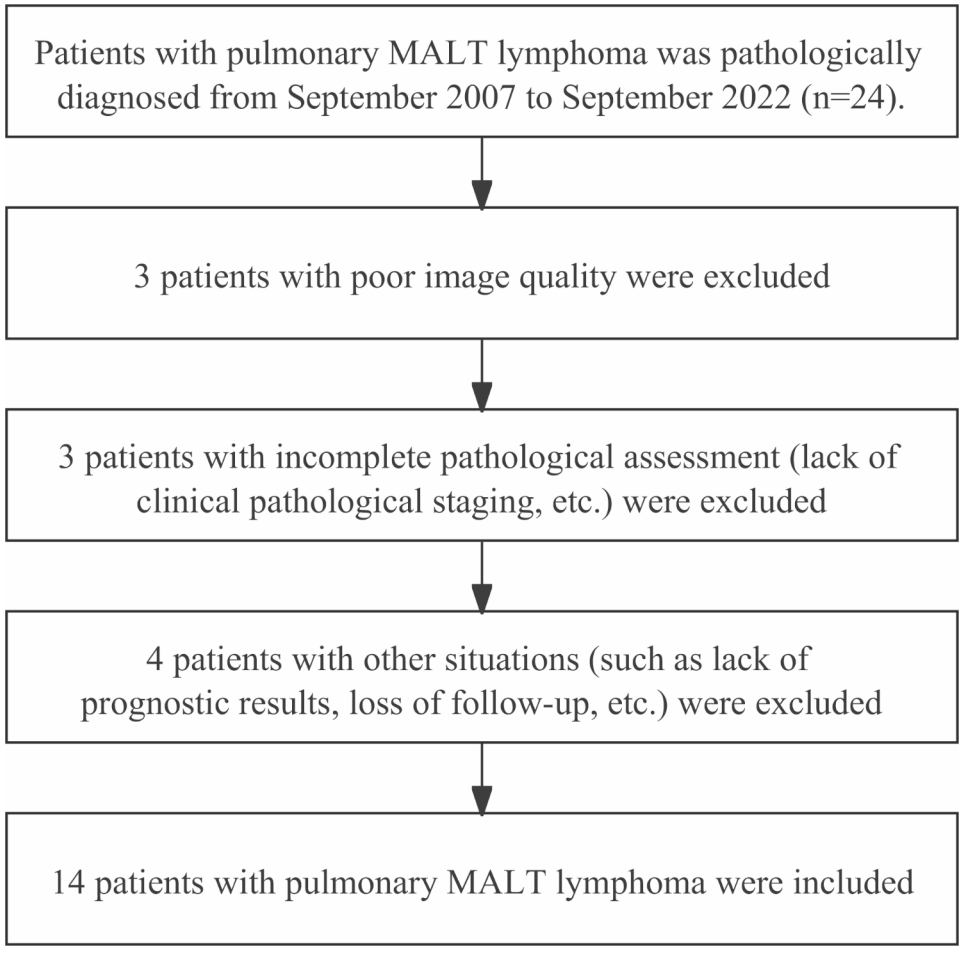

Fig. 1 The flowchart of case collection

follow-up date or the date of death. Survival rate differences among the patient groups were evaluated using the Log-rank test. All tests were two-sided, and a P-value of <0.05 was deemed to indicate statistical significance.

Results

Clinical characteristics

The clinical characteristics of the 14 MALT lymphoma patients are detailed in Table 1. The male-to-female ratio of the patients was 5:9. The median age at diagnosis was 60 years (range 44–81 years). Nine patients (64.29%) were younger than 60 years. Ten patients (71.43%) had a good performance status score, and 2 patients (14.29%) had a history of smoking. Apart from 8 patients (57.14%) with no history of immunodeficiency diseases, 1 patient (7.14%) had Systemic Lupus Erythematosus (SLE), 1 patient (7.14%) had hepatitis B, 2 patients (14.29%) had hypertension, and 2 patients (14.29%) had diabetes. Besides 6 asymptomatic patients (42.86%), respiratory symptoms manifested as cough (50.00%), expectoration (35.71%), chest tightness (14.29%), dyspnea (21.43%), and chest pain (28.57%). Four patients (28.57%) experienced weight loss, and 1 patient (7.14%) presented with fever as a clinical symptom. Nine patients (64.29%) had hemoglobin levels below 120 g/L.

CT findings

A total of 27 lesions were observed in 14 patients with pulmonary MALT lymphoma, including 11 cases with unilateral lesions and 3 cases with bilateral lesions. Lesion types were solitary nodules/masses in 10 cases, multiple nodules/masses in 3 cases, and pneumonia-like in 1 case. The average size of the masses was 36.25 ± 23.68 cm^2. Bronchiectasis was associated with 9 cases, pleural effusion with 2, mediastinal lymph node enlargement in 1, and bronchogram signs in 9. Additionally, 3 cases presented with ground-glass nodules (GGO), as detailed in Table 2; examples of imaging are provided in Figs. 2 and 3. The radiological features of pulmonary MALT lymphoma were diverse and non-specific, including bronchial signs, nodular shadows, pulmonary consolidation, and ground-glass opacities, complicating differential diagnosis from lung cancer, tuberculosis, and pneumonia.

Table 1 Clinical data of all pulmonary MALT lymphoma patients

Characteristics	Patients *n*(%)
Gender(male/female)	5(35.71%)/9(64.29%)
Median age (years)(range)	60(44–81)
≥60/<60	5(35.71%)/9(64.29%)
PS(0–1/2–5)	10(71.43%)/4(28.57%)
Smoking history	2(14.29%)
Background of immune deficiency	
SLE	1(7.14%)
Hepatitis B	1(7.14%)
Hypertension	2(14.29%)
Diabetes	2(14.29%)
None	8(57.14%)
Respiratory symptoms	
Cough	7(50.00%)
Expectoration	5(35.71%)
Chest tightness	2(14.29%)
Shortness of breath	3(21.43%)
Chest pain	4(28.57%)
No symptoms	6(42.86%)
Clinical symptoms	
Loss of weight	4(28.57%)
Fever	1(7.14%)
No symptoms	10(71.43%)
Hemoglobin	
≥120 g/L	5(35.71%)
<120 g/L	9(64.29%)

Abbreviations MALT, mucosa-associated lymphoid tissue; SLE, Systemic Lupus Erythematosus

Table 2 The patient's chest CT findings

CT Features	Patients
a Location, n (%)	
Left upper lobe lung	6(42.86%)
Left middle lobe lung	1(7.14%)
Left lower lobe lung	3(21.43%)
Right upper lobe lung	8(57.14%)
Right middle lobe lung	6(42.86%)
Right lower lobe lung	3(21.43%)
b Laterality, n (%)	
Unilateral	11(78.57%)
Bilateral	3(57.14%)
c Lesion type, n (%)	
Single nodule	10(71.43%)
Multiple nodule	3(21.43%)
Pneumonia-like consolidation	1(7.14%)
d Nodule size(cm^2) Mean ± SD (range)	36.25 ± 23.68(8.57–94.56)
e Bronchiectasis, n (%)	
Yes	9(64.29%)
No	5(35.71%)
f Pleural effusion, n (%)	
Yes	2(14.29%)
No	12(85.71%)
g Mediastinal lymph node enlargement, n (%)	
Yes	1(7.14%)
No	13(92.86%)
h Air bronchography sign, n (%)	
Yes	9(64.29%)
No	5(35.71%)
i GGO, n (%)	
Yes	3(21.43%)
No	11(78.57%)

Abbreviations CT: Computed Tomography; SD, standard deviation; GGO, ground-glass nodule

Pathological features

At admission, 7 patients were diagnosed with lung infection, 3 with lung cancer, 2 with tuberculosis, 1 with lymphoma, and 1 with diffuse interstitial lung disease. Pathological evaluations were conducted on all 14

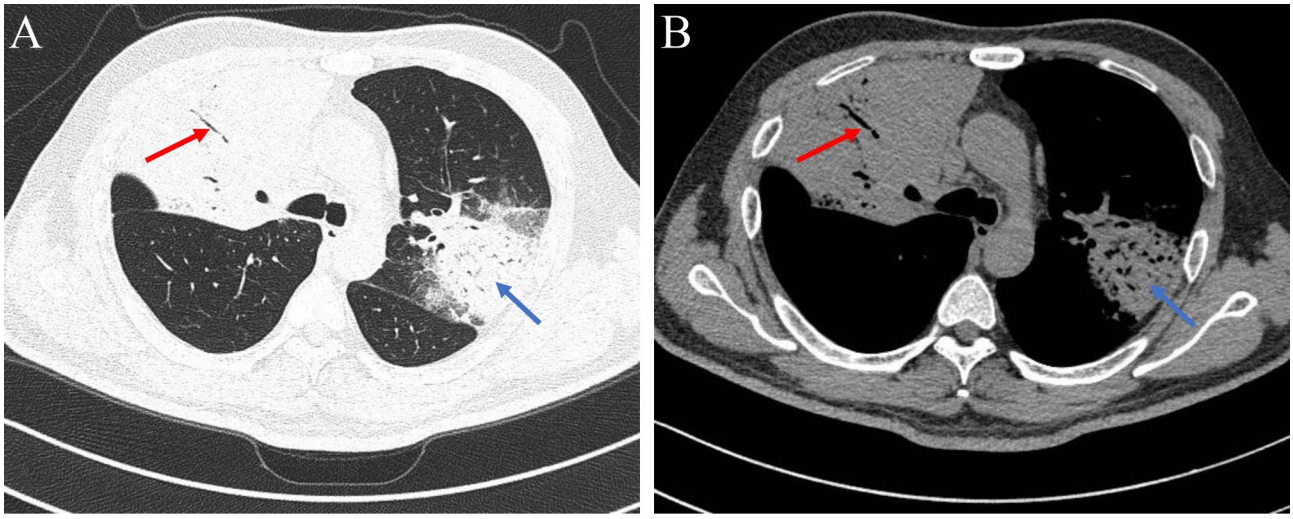

Fig. 2 Pulmonary MALT lymphoma in a 50-year-old man. **A**: Lung window showing consolidation with air bronchogram sign (red arrow), and a ground-glass nodule in the upper lobe of the left lung (blue arrow); **B**: Mediastinal window showing consolidation with air bronchogram sign (red arrow), and a ground-glass nodule in the upper lobe of the left lung (blue arrow)

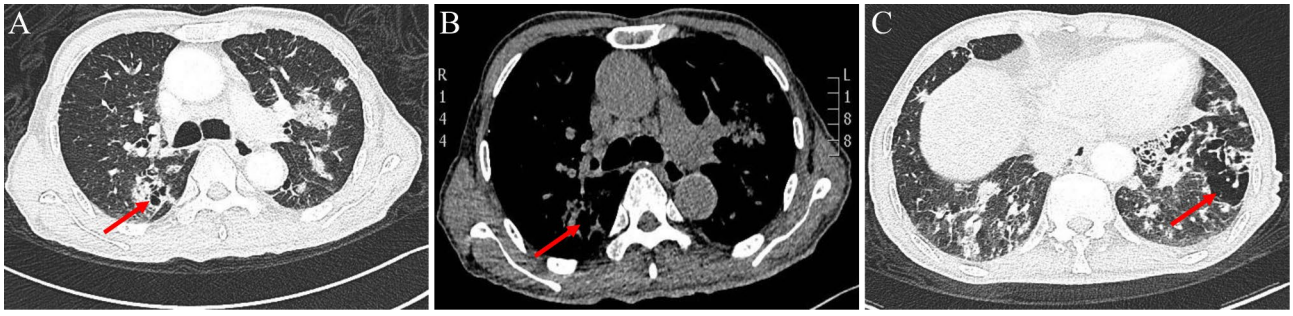

Fig. 3 Pulmonary MALT lymphoma in a 81-year-old woman. **A**: Lung-diaphragmatic window showing cystic bronchiectasis within the lesion in the lower lobe of the right lung (red arrow); **B**: Mediastinal window showing cystic bronchiectasis within the lesion in the lower lobe of the right lung (red arrow); **C**: Lung window showing cystic bronchiectasis within the lesion in the upper lobe of the left lung (red arrow)

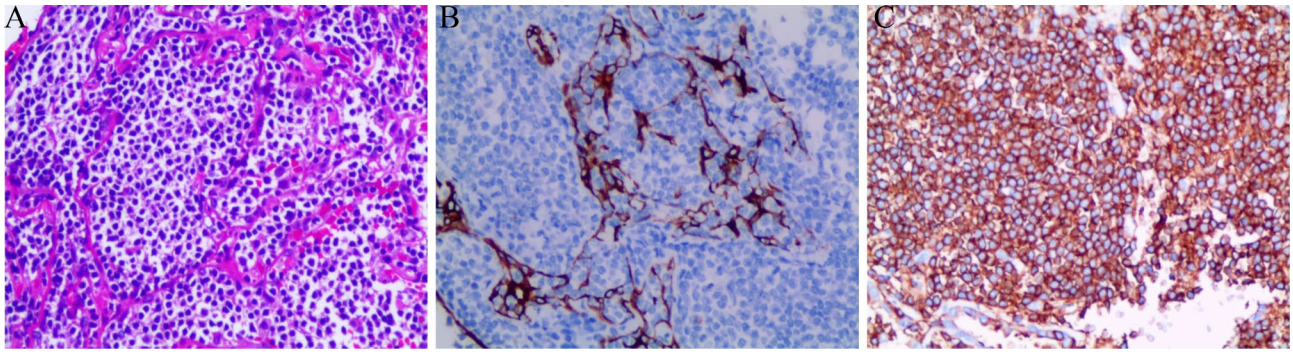

Fig. 4 Pathological findings of patients with lung MALT lymphoma. **A**: Microscopically diffuse small lymphocyte infiltration (H&E ×100). **B**: Immunohistochemistry showed positive CK(epithelial +) .**C**: Immunohistochemistry was positive for CD20

Table 3 The patient's pathological feature

Features	Patients
Diagnosis on admission, n (%)	
Pulmonary infection	7(50.00%)
Lung cancer	3(21.43%)
Pulmonary tuberculosis	2(14.29%)
lymphoma	1(7.14%)
Diffuse interstitial lung disease	1(7.14%)
Diagnostic method, n (%)	
TBLB	8(57.14%)
CT-guided percutaneous lung biopsy	2(14.29%)
Exairesis	4(28.57%)
Immunohistochemistry, n (%)	
CD20(+)	14(100%)
Ki-67(+)	14(100%)
CD5(+)	10(71.43%)
CD10(+)	9(64.29%)
Bcl-2(+)	11(78.57%)
CK(epithelial +)	9(64.29%)
CD3(-)	14(100%)
CD23(-)	14(100%)
CyclinD1(-)	14(100%)

Abbreviations TBLB: transbronchial lung biopsy; CT: Computed Tomography

patients, utilizing bronchoscopic biopsy in 8 cases, CT-guided percutaneous lung biopsy in 2, and surgical resection in 4. Microscopic examination of the pathological specimens from all 14 patients revealed diffuse uniform small lymphocytic proliferation with infiltration, evidence of epitheliotropism, relatively abundant cytoplasm with some clarity, round or irregular nuclei, and some without visible nucleoli (Fig. 4). Immunohistochemistry: Lymphoma cells showed positive expression for CD20, and most showed positive expression for CD5, CD10, Bcl-2, CK (epithelial +). Ki-67 index ranged from 3 to 30%. CD3, CD23, CyclinD1 all showed negative expression. Details are presented in Table 3.

Treatment

Of the cohort, 2 patients opted to leave the hospital without receiving any treatment for various reasons. The remaining 12 patients were administered diverse therapeutic regimens: 2 underwent lobectomy; 6 were treated with chemotherapy alone; and 4 received a combination of chemotherapy and surgical intervention. Specifically, 6 patients were treated with the R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), three patients with the CHOP chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone), and one

patient with the R-CVP chemotherapy regimen (doxorubicin, cyclophosphamide, vincristine, and prostaglandin E1). No patients underwent radiation therapy. The treatment efficacy was evaluated as complete remission (CR) in seven patients, partial remission (PR) in four patients, and stable disease in one patient.

Prognosis

Three patients experienced disease progression or relapse post-treatment, and two deaths were recorded (causes unspecified), over a median follow-up period of 87 months (ranging from 12 to 192 months). Kaplan-Meier survival analyses, illustrated in Fig. 5A and B, estimated 5-year and 10-year overall survival (OS) rates at 91.67% and 76.39%, respectively, with a median progression-free survival (PFS) of 7 years. Additionally, Fig. 5C shows that there was no statistically significant difference in PFS between the chemotherapy group and the chemotherapy plus surgery group ($P=0.22$).

Discussion

Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma, often termed bronchial MALT lymphoma, is known to arise from the bronchial mucosa's lymphoid tissue. Despite being the predominant form of primary pulmonary lymphoma, it is notably rare, with a reported incidence of 1.59 cases per 100,000 individuals [10, 11]. This rarity could stem from the absence of bronchus-associated lymphoid tissue in the lungs of healthy adults [12, 13]. Previous studies suggest that the occurrence of pulmonary MALT lymphoma is due to long-term exposure to various antigens, such as chronic inflammation, smoking, and immunodeficiency diseases like rheumatoid arthritis, Sjögren's syndrome, etc., though its exact pathogenesis remains unclear [14, 15]. In this study, 14.29% of patients had a history of smoking, which is lower than other studies [6, 16], indicating that exposure to tobacco smoke may be associated with pulmonary MALT lymphoma. Another noteworthy finding in our study is that 14.29% of patients had a history of diabetes. The disease exhibits indolent behavior, is long-standing, and progresses slowly, commonly seen in middle-aged and elderly individuals. The median age in this study was 60 years, similar to other studies [17, 18]. Our study also found that the disease is more prevalent in females, consistent with related literature reports [11, 19]. The malignancy is low-grade with a long disease history, and clinical symptoms depend on the extent and location of the lesion, lacking specificity. In our study, 57.14% of patients had clinical symptoms, manifesting as nonspecific pulmonary symptoms like cough, expectoration, chest pain, dyspnea, chest tightness, etc. Additionally, 28.57% of patients experienced weight loss and 14.29% had fever and other systemic symptoms. Most patients had a good performance status score, and although 64.29% had reduced hemoglobin levels, most patients did not have adverse prognostic factors, confirming the indolent clinical features of pulmonary MALT lymphoma.

Radiological evaluations of pulmonary MALT lymphoma typically reveal a spectrum of presentations, including nodular formations, masses, consolidations, and mixed types. These abnormalities may affect either a single lung lobe or both lungs, often manifesting as nodular or patchy shadows within the lung parenchyma [17, 20]. In this study, radiological manifestations of pulmonary MALT lymphoma included: solitary nodules/masses in 10 cases, multiple nodules/masses in 3 cases, unilateral lesions in 11 cases, bilateral in 3 cases, accompanied by bronchiectasis in 9 cases, and mediastinal lymph node enlargement in 1 case, primarily presenting as pulmonary nodules and masses or mass-like consolidation areas, with mediastinal lymph node enlargement and pleural effusion being rare, consistent with previous studies [6, 21, 22]. This indicates the diverse morphological characteristics of pulmonary MALT lymphoma lesions, with non-specific radiological manifestations that are easily misdiagnosed. Pathology and immunohistochemistry are key to diagnosing the disease. However, as the lesions are

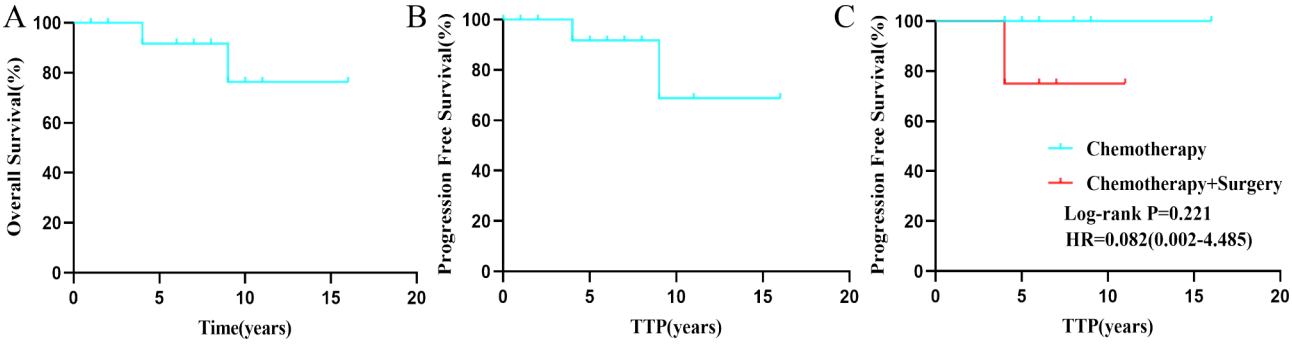

Fig. 5 MALT lymphoma Patients' Survival Curves. **A**: OS curve for 14 patients; **B**: Kaplan-Meier estimate of PFS for 14 patients; **C**: PFS survival curves for the chemotherapy group and the chemotherapy plus surgery group. *Abbreviations* TTP: Time to progression; OS: Overall Survival; PFS: Progression Free Survival

often localized in the lungs, obtaining pathological specimens can be relatively challenging, leading to initial misdiagnosis as tuberculosis, lung infection, lung cancer, etc., making timely pathological examination crucial for accurate diagnosis. In our study, bronchoscopic biopsies diagnosed 8 cases, CT-guided percutaneous lung puncture biopsies accounted for 2, and surgical resection provided the pathological basis for 4 cases. Histologically, these specimens showed diffuse proliferation of uniformly small lymphocytes with infiltration, characterized by epitheliotropism, cytoplasmic abundance with a degree of transparency, round or irregularly shaped nuclei, and the presence of both neoplastic and reactive follicles indicative of follicular colonization [23]. This epitheliotropic feature is unique to MALT lymphoma cells. From an immunohistochemical perspective, pulmonary MALT lymphoma is rooted in the B cells of the marginal zone, evidenced by the strong CD20 expression in lymphoma cells across all 14 patients. Additionally, Ki-67 expression was positive in all cases, with indices ranging between 3% and 30%. Expressions of CD3, CD23, and CyclinD1 were uniformly negative, highlighting the distinct immunophenotypic profile of pulmonary MALT lymphoma.

Treatment strategies for pulmonary MALT lymphoma encompass surgery, chemotherapy, molecular targeted therapy, radiotherapy, and watchful waiting. Our study aligns with prior evidence, demonstrating favorable clinical outcomes across different treatment modalities: complete remission (CR) was achieved in 7 out of 12 treated patients, partial remission (PR) in 4, and stable disease (SD) in 1 case [6, 24]. Despite the lack of a universally accepted treatment protocol, there is a growing consensus against prioritizing surgery to conserve lung functionality [25–27]. Comparative analyses of overall survival rates between chemotherapy and surgical intervention have shown negligible differences [6, 17], yet research by Lee et al. and Vanden Eynden et al. suggests surgical resection might benefit patients with early-stage disease [28, 29]. Additionally, Some scholars suggest active and close monitoring without immediate treatment for low-grade primary pulmonary MALT lymphoma [30]. In our study, only 2 patients underwent surgery alone, 6 received chemotherapy alone, and 4 received combined chemotherapy and surgery, with most patients undergoing chemotherapy. Due to potential complications such as radiation pneumonitis, no patients received radiotherapy. Our study observed that 3 patients experienced progression or relapse after treatment, and 2 patients died. The estimated 5-year and 10-year OS rates were 91.67% and 76.39%, respectively, consistent with related studies [6, 31, 32], again indicating that pulmonary MALT lymphoma is indolent, progresses slowly, and generally has a favorable prognosis. Additionally, our study found no significant difference in PFS between chemotherapy alone and combined chemotherapy and surgery ($P=0.22$), suggesting that, to minimize surgical trauma and preserve lung function as much as possible, surgery may not be the preferred treatment modality for pulmonary MALT lymphoma, a conclusion supported by previous research [6, 33].

This investigation is limited by its small sample size, single-center design, and the short follow-up period for some participants. Being retrospective, the conclusions drawn necessitate further validation through multicenter, large-scale clinical studies.

Conclusion

In conclusion, our findings reiterate that pulmonary MALT lymphoma is a typically indolent pathology, prone to slow progression and characterized by a generally optimistic prognosis. However, the risk of misdiagnosis remains high. Accurate diagnosis hinges on pathological evaluation and immunohistochemical analysis. While surgery could be considered for both diagnosis and treatment, chemotherapy emerges as the preferable approach to minimize surgical impact and conserve lung function, thereby avoiding overtreatment.

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None declared.

Author contributions

Qiuling Liao: Project development, Data Collection, Manuscript writing and MR scan. Qilin Yu and Cheng Yu: Data Collection.Minping Zhang: Data analysis. Enhua Xiao: Project guidance, Data collection, Data analysis, Manuscript editing.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Research involving human participants and/or animal

The protocols and procedures were approved by the institutional review board of the Second Xiangya Hospital of Central South University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The written informed consent form for this study was provided by the participants themselves or their legal guardians.

Consent for publication

All authors give consent for publication.

Conflict of interest

The authors affirm that there are no known competing financial interests or personal relationships that could be perceived as influencing the findings presented in this manuscript.

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